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Beta-Agonists And Death From Asthma (Correspondence)

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The Use Of Beta-Agonists And The Risk Of Death And Near Death From Asthma (Original Articles)

Spitzer, Walter O.; Suissa, Samy; Ernst, Pierre; Horwitz, Ralph I.; Habbick, Brian; Cockcroft, Donald; Boivin, Jean-Francois; McNutt, Mary ; Buist, A. Sonia; Rebuck, Anthony S.
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Abstract

Background. Morbidity and mortality from asthma appear to be increasing, and it has been suggested that medications used to treat asthma are contributing to this trend. We investigated a possible association between death or near death from asthma and the regular use of beta(sub 2)-agonist bronchodilators.

Methods. Using linked health insurance data bases from Saskatchewan, Canada, we conducted a matched case-control study of subjects drawn from a cohort of 12,301 patients for whom asthma medications had been prescribed between 1978 and 1987. We matched 129 case patients who had fatal or near-fatal asthma with 655 controls (who had received medications for asthma but had not had fatal or near-fatal events) with respect to region of residence, age, receipt of social assistance, and previous hospitalization for asthma.

Results. The use of beta-agonists administered by a metered-dose inhaler was associated with an increased risk of death from asthma (odds ratio, 2.6 per canister per month; 95 percent confidence interval, 1.7 to 3.9) and of death or near death from asthma, considered together (odds ratio, 1.9; 95 percent confidence interval, 1.6 to 2.4). For death from asthma, use of the beta-agonist fenoterol was associated with an odds ratio of 5.4 per canister, as compared with 2.4 for the beta-agonist albuterol. On a microgram-equivalent basis, the odds ratio for this outcome with fenoterol was 2.3, as compared with 2.4 with albuterol.

Conclusions. An increased risk of death or near death from asthma was associated with the regular use of inhaled beta(sub 2)-agonist bronchodilators, especially fenoterol. Regardless of whether beta-agonists are directly responsible for these adverse effects or are simply a marker for more severe asthma, heavy use of these agents should alert clinicians that it is necessary to reevaluate the patient's condition. (N Engl J Med 1992;326:501-6.)

TEXT

In April 1989, investigators from New Zealand reported the results of a case-control study in which the use of fenoterol, a selective beta(sub 2)-agonist, was found to be associated with an increased risk of death from asthma (Ref. 1). The study found no similar increase in risk for albuterol, the other beta-agonist widely used in New Zealand. These findings engendered controversy, because the studies were considered subject to bias from several sources, including imbalances in the selection of controls and in the collection of data on exposure to bronchodilators, as well as inadequate adjustment for differences in the severity of asthma.

In response to this concern, the investigators have reported the results of two further case-control studies (Ref. 2,3). In these studies, which minimized the bias due to the selection of controls and data collection, an association with death from asthma was again found for fenoterol, but not for albuterol. The controversy has been heightened by the recent report that regular use of fenoterol, as compared with ''as needed'' use, was associated with a deterioration in the control of asthma symptoms (Ref. 4). A major unresolved question was whether the associations observed with the use of fenoterol were also present with other beta(sub 2)-agonists.

The Saskatchewan Asthma Epidemiology Project was planned to address many of these uncertainties (Ref. 5). Specifically, we asked whether regular, long-term use of beta-agonists in general, and of fenoterol in particular, was associated with an increased risk of death or near death from asthma. In conducting this research, we used the health insurance data bases of the province of Saskatchewan, where the population of 1.1 million is insured for the cost of most hospital and ambulatory care and the cost of prescription drugs. The Saskatchewan data bases, which permit one to link information from different sources for each person, have been described in detail elsewhere (Ref. 6,7).

Methods

Source and Eligibility of Study Subjects

We began by examining the computerized files of the Saskatchewan Prescription Drug Plan, which held just over 20 million prescriptions for drugs listed in the Saskatchewan formulary that had been dispensed to eligible residents of the province 5 to 54 years of age between 1980 and 1987. Subjects outside this age range were not included because of the greater likelihood that drugs prescribed for them were for conditions other than asthma. We identified 68,813 beneficiaries of the plan who had received at least one prescription medication commonly used to treat asthma during these years. These drugs were fenoterol, albuterol, metaproterenol, terbutaline, any compound of theophylline, ipratropium bromide, cromolyn, and inhaled beclomethasone. We then included all drugs prescribed for these patients during the period 1978 through 1987 and identified 12,301 patients for whom at least 10 prescriptions for one or more of the asthma drugs had been dispensed over the 10-year period. Within this geographically defined cohort, we established the dates that further identified the available members of the cohort. The date on which each subject entered the cohort was defined as the date of the subject's 10th dispensed prescription, the subject's fifth birthday, or January 1, 1980, whichever was latest. The date of a subject's exit from the cohort was the subject's 55th birthday, the date of the outcome event (death or near-fatal asthma), the date of the subject's emigration from the province, or April 30, 1987, whichever was earliest.

Outcomes and Identification of Case Patients

The case patients were subjects within the cohort who met predetermined criteria for near-fatal asthma or death from asthma during the years 1980 through 1987. If a subject who died of asthma had previously had a near-fatal episode, the death was chosen as the outcome for analysis.

The primary hypothesis concerned the association of near deaths plus deaths, treated as a combined outcome measure, with exposure to any beta-agonist dispensed by a metered-dose inhaler.

We searched the data base to identify all the deaths among the 12,301 members of the cohort. Death certificates, coroners' reports, autopsy reports, and hospital-discharge summaries were obtained for all these deaths. Of 180 deaths identified, no documents were found for 15. Three physicians with special expertise in asthma reviewed all available information about the 165 deaths independently and categorized each as being probably due to asthma, possibly due to asthma, or not likely to be due to asthma. The consultants were blinded to the medications used and to the identity of the patients. They classified 44 deaths as probably due to asthma, reaching complete agreement independently for 40 of them and by consensus for the remaining 4.

Patients were classified as having near-fatal asthma if they had hypercarbia (arterial partial pressure of carbon dioxide above 6.0 kPa 45 mm Hg]), nonelective intubation during an acute asthma attack, or both. To identify episodes of asthma that might meet these criteria, we searched the data bases for procedure or billing codes corresponding to cardiopulmonary resuscitation, airway intubation, or assisted ventilation in hospitalized members of the cohort whose discharge diagnoses suggested airway disease (codes 490 to 493 and 496 of the International Classification of Diseases, 9th Revision, Clinical Modification) (Ref. 8). In addition, the medical charts of patients hospitalized for asthma for five days or more at six large referral hospitals were examined. For 99 percent of the hospitalizations of the 964 subjects with potential episodes of near-fatal asthma, hospital-discharge summaries and laboratory results were obtained. Eighty-five subjects were identified as having had one or more probable episodes of near-fatal asthma; the three consultants reached complete agreement independently for 80 of them and by consensus for the remaining 5. A subject's most recent near-fatal episode was used when more than one such episode was identified.

Selection of Controls

Up to eight controls for each case patient were selected randomly within the cohort after they were matched with respect to the following variables: region of residence, receipt of social assistance at any time during the study, age at entry into the cohort, date of entry, and hospitalization at least once in the two years before the event. In addition, the controls were required to have been at risk for the outcome at the time of the event in the case patient, a date we refer to as the index date.

Exposure to Asthma Medications

The principal risk factor examined was long-term use of inhaled beta(sub 2)-agonists delivered by a metered-dose inhaler. We defined long-term use as the use of a drug during the 12 months preceding the index date. The data base also permitted us to count accurately the number of prescriptions dispensed for any of the drugs under study, month by month. We therefore computed the number of units dispensed during the 12 months before the index date, with one unit defined as the amount of beta-agonist dispensed by one metered-dose inhaler per month. When a medication was dispensed as a dry powder or nebulizer solution, one unit was the dose usually prescribed per month. For the other asthma drugs (e.g., oral beta-agonists, theophylline, corticosteroids, and the like), one unit referred to an actual dispensed prescription.

Ascertainment of Adjustment Variables

Data on the use of health services and concomitant medications were obtained to adjust for possible differences between the case patients and the controls. The health insurance files for the case patients and the controls provided a record of their use of health services. From these files we calculated the number of hospitalizations for asthma for each

study subject and the number of visits to a physician in the two years before the index event. The use of drugs other than those to treat asthma was also established from the files of the prescription-drug plan. We grouped these drugs into four categories: (1) cardiac medications, including antihypertensive and potassium-sparing diuretic agents; (2) neurologic drugs, including anticonvulsants, antidepressants, and major tranquilizers; (3) drugs relatively contraindicated in asthma, specifically beta-blockers, sedatives, and parasympathomimetic agents; and (4) non-potassium-sparing diuretic agents. An index of risk was created, representing the number of categories of concomitant therapy received.

Statistical Analysis

We initially carried out a bivariate analysis that estimated crude matched odds ratios; in fact, these were adjusted for the four matching factors with use of conditional logistic regression (Ref. 9). Multiple conditional logistic regression for matched sets, (Ref. 10) with a variable number of controls per case patient, was used to estimate the adjusted odds ratios for the independent effects of the various asthma medications. The frequency of use, measured in units, of the two principal beta-agonists taken by metered-dose inhaler over the 12-month period, was quantified in three different ways. First, exposure was classified as being present or absent (a dichotomous variable). Second, exposure was categorized ordinally in the following four classes, according to the number of metered-dose inhalers used over the 12 months: 0, 1 to 12, 13 to 24, or 25 or more. Third, exposure was quantified as the number of units used per month, with the resulting continuous dose-response odds ratio measuring the increase in risk per unit per month. For the other asthma medications, we used both the dichotomous and the continuous classifications.

Because the only formulation of albuterol available in a metered-dose inhaler contained 100 microg per inhalation, as compared with 200 microg in each inhalation from the fenoterol inhaler, the odds ratios were also calculated with the assumption that one unit of fenoterol was equivalent to two units of albuterol. This was done by dividing the regression coefficients by 2, and since the logistic model used in the odds ratios was log-linear, the square root of the coefficient provided the appropriate estimate of effect.

The goodness of fit of the regression models, particularly the continuous dose-response model, was addressed in two ways. First, the assumption of log-linearity for the per-unit odds ratios was evaluated by comparing the fitted values from the continuous model with the values of the odds ratios estimated from the ordinal model. Second, the stability of the odds ratios was verified by assessing the effect of removing influential observations (Ref. 11). For all the results presented, the goodness-of-fit and stability evaluations of the regression models resulted in fluctuations of the estimated odds ratios of +/- 20 percent at most, well within the magnitude of the random error. Finally, some regression models were made parsimonious by removing variables that had no effect on the odds ratios of interest, thus improving their precision. Two-tailed 95 percent confidence intervals are provided for each odds ratio.

Peer Review

Because this study was funded entirely by Boehringer-Ingelheim Pharmaceuticals, which has a commercial interest in one of the products assessed, the investigators and the sponsor agreed on a verifiable peer-review process. Accordingly, a Scientific Advisory Board was created that reviewed the protocol in February 1990 after determinations of feasibility had been done, but before field work had begun. The chairman of the advisory board assessed and documented changes made in the interim by the investigators and circulated them to the entire board. The board reviewed the main results, conclusions, and interpretations of the data in June 1991.

Results

Table 1 shows selected characteristics of the study subjects. Overall, the case patients and the controls were similar with respect to age and sex. As compared with the controls, the case patients were hospitalized more frequently and used the services of physicians more often. They also used several classes of medications other than asthma drugs more often, a difference that was more pronounced when only the subjects who died from asthma were considered. When concomitant medications were combined into an aggregate index, their use was more frequent among the case patients who died of asthma (odds ratio, 2.2; 95 percent confidence interval, 1.0 to 4.9). In subsequent analyses, the odds ratios were adjusted for differences in the number of hospitalizations and in the index for the aggregate use of other medications, but not for the number of visits to a physician, because this factor did not prove to be important in any analysis. *Table 1. Selected Characteristics of Study Subjects Who Died of Asthma or Had Near-Fatal Asthma *. **TABLE OMITTED**

The relation between the use of asthma medications and the risk of fatal or near-fatal asthma is shown in Table 2. In this table, frequencies of exposure to asthma medications are shown in an unmatched format for the case patients and the controls, with unadjusted matched odds ratios calculated. In addition, odds ratios and 95 percent confidence intervals were calculated by multivariate matched techniques, including adjustment for the use of other asthma medications, as well as for the number of hospitalizations and the index of use of concomitant medication. *Table 2. Matched Odds Ratios for Exposure to Asthma Medication in the Subjects with Fatal or Near-Fatal Asthma, during the 12 Months before the Index Date *. **TABLE OMITTED**

In this analysis, the adjusted matched odds ratios indicated that both fenoterol and albuterol taken by metered-dose inhaler were associated with an increased risk of death from asthma or near-fatal asthma, as well as with an increased risk of death alone. An increased risk of death or near-fatal asthma was also found for albuterol taken by nebulizer and for other inhaled beta-agonists, theophylline, and oral corticosteroids. No increase in risk was noted for the use of inhaled corticosteroids and cromolyn, considered together. The results were similar when deaths from asthma were considered alone, except that there was no increase in risk associated with the use of oral corticosteroids.

In the comparison of crude and adjusted matched odds ratios, an important point is apparent about the association between the use of inhaled albuterol and the risk of death from asthma. In Table 2, the crude matched odds ratio for albuterol was 0.9, but it increased to 2.8 after adjustment for the use of fenoterol. As Table 3 shows, this increase occurred because the odds ratio for albuterol was 1.2 among the patients who also used fenoterol and 3.7 among those who did not. When the odds ratio was calculated with adjustment for fenoterol use and other factors, the overall increase in risk for albuterol -- to an odds ratio of 2.8 (Table 2) -- became clinically important and statistically significant. The data in Table 3 also explain why previous studies found a spurious protective odds ratio for albuterol. When the analysis was restricted to patients who used albuterol or fenoterol but not both, the crude odds ratios were 3.7 for fenoterol and 0.3 for albuterol -- i.e., reciprocal ratios. *Table 3. Relation of Albuterol Use to the Incidence of Death from Asthma, with Adjustment for Use of Fenoterol *. **TABLE OMITTED**

Table 4 refines the analysis of the delivery of fenoterol and albuterol by metered-dose inhaler by using an ordinal classification of exposure. In this analysis, the categories were the numbers of dispensed units of either drug over a 12-month period (0, 1 to 12, 13 to 24, and 25 or more). When an odds ratio of 1.0 was assigned to the reference category of no use, the values for death from asthma and near-fatal asthma combined ranged from 4.1 to 21.5 for fenoterol and were statistically significant. Similar results were found for albuterol. In the analysis of death from

asthma the drugs were comparable, except that there were higher odds ratios for fenoterol at higher levels of exposure. In this ordinal analysis of exposure, the increasing gradient in risk with increasing use of beta(sub 2)-agonists is clear. Patients who received more than two metered-dose inhalers per month on average had a very large excess risk of death or near-fatal asthma or of death alone. Fenoterol was available only in doses of 200 microg per inhalation, and albuterol only in 100-microg doses. So that the two medications can be compared on a weight-for-weight basis, Table 4 also includes an ordinal analysis of exposure in which the number of inhalers of fenoterol was reduced by half. *Table 4. Adjusted Matched Odds Ratios for Inhaled Fenoterol or Inhaled Albuterol in the Subjects with Fatal or Near-Fatal Asthma during the 12 Months before the Index Date, According to an Ordinal Classification of Exposure *. **TABLE OMITTED**

Table 5 shows the odds ratios for each additional unit of inhaled beta-agonists dispensed per month. As estimated from a regression model, the odds ratios for any inhaled beta-agonist were 1.9 for death and near-fatal asthma and 2.6 for death alone. In a separate model, the odds ratios for each unit of fenoterol were 2.3 for death and near-fatal asthma and 5.4 for death only; for albuterol, the odds ratios were 1.9 and 2.4, respectively. *Table 5. Adjusted Matched Odds Ratios for Inhaled Fenoterol or Albuterol in the Subjects with Fatal or Near-Fatal Asthma during the 12 Months before the Index Date, According to Models of Continuous Exposure *. **TABLE OMITTED**

The analysis based on continuous exposure in Table 5 enabled us to compare the use of 100 microg of fenoterol with the use of 100 microg of albuterol. In this weight-for-weight analysis, the odds ratio for fenoterol was 1.5 for death and near death combined, similar to the odds ratio of 1.9 for albuterol. Similarly, for death alone, the odds ratio of 2.3 for fenoterol was almost indistinguishable from the value of 2.4 for albuterol.

We also looked at the use of beta-agonists among subjects thought to be at low risk. Among those not hospitalized for asthma in the previous two years, the odds ratios for death from asthma remained significantly elevated for both albuterol (2.4; 95 percent confidence interval, 1.3 to 4.7) and fenoterol (2.1; 95 percent confidence interval, 1.0 to 4.7).

In this cohort there were 47,842 person-years of follow-up. To estimate the absolute risks of death from asthma in a population of patients with asthma, we used the distribution of exposure in the 655 controls to approximate the person-time during which fenoterol and albuterol administered by metered-dose inhaler were used (Ref. 12). The overall rate of death from asthma was 9.2 per 10,000 person-years (95 percent confidence interval, 6.8 to 12.4). The rate for fenoterol was 34.6 (95 percent confidence interval, 21.4 to 56.1), whereas the rate for albuterol was 8.6 per 10,000 person-years (95 percent confidence interval, 5.9 to 12.6). For those not taking either of these two inhaled beta-agonists, the rate of death from asthma was 1.8 per 10,000 person-years (95 percent confidence interval, 0.4 to 7.5). These absolute rates are crude and therefore unusable; any comparisons between them do not take into account differences with respect to doses and other factors associated with the risk of death from asthma.

Discussion

In a case-control study of subjects drawn from a population-based cohort, we found that the use of inhaled beta-agonist bronchodilators, principally fenoterol and albuterol, was associated with an increased risk of the combined outcome of fatal and near-fatal asthma, as well as of death from asthma alone.

When investigators earlier reported an increase in mortality from asthma in various countries around the world, the explanations focused on newly introduced treatments (Ref. 13). The case-control studies from New Zealand emphasized the possible role of one particular bronchodilator, fenoterol, while suggesting that other bronchodilators did not similarly

increase the risk of death from asthma (Ref. 1-3). Our study reveals that the use of beta-agonist drugs as a class, not just that of fenoterol alone, is associated with an increased risk of death from asthma. Furthermore, the use of theophyllines, another commonly used class of bronchodilators, was also associated with an excess risk of a major adverse event. On the other hand, the antiinflammatory agents cromolyn and inhaled corticosteroids were not associated with such a risk.

An important advantage of our study was the availability of data on the number of metered-dose inhalers dispensed per month. These data permitted detailed dose-response analyses for the two beta-agonist agents most commonly used. The increased risk of fatal and near-fatal asthma with the use of albuterol and fenoterol was clinically important for patients who used one to two canisters per month. For patients who used more than two canisters monthly, both bronchodilators were associated with a greatly increased risk, which was especially marked for fenoterol.

At the time of the study, canisters of fenoterol in Saskatchewan contained 200 inhalations, each of 200 microg of drug, whereas those of albuterol contained 200 inhalations, each of 100 microg. Because different formulations are available elsewhere (100 microg of fenoterol and 200 microg of albuterol), we examined the risk associated with these two medications on a weight-for-weight basis. This analysis suggested a similar risk of death per 100 microg of either drug. The validity of such a weight-equivalence approach has been supported by in vitro (Ref. 14,15) and in vivo (Ref. 16,17) studies, as well as by clinical research (Ref. 18-20).

One limitation of our study was that the only data available with which to adjust for the severity of asthma were those from the computerized data bases. Fieldwork to collect relevant data from hospitals and physicians in Saskatchewan may permit further adjustment for severity. Thus, it remains plausible that many of the drugs for asthma appear to increase risk because the patients for whom asthma medications are prescribed are more likely to die from their more severe asthma. However, even among subjects at low risk who were not hospitalized in the two years before the index event, both albuterol and fenoterol were associated with a doubling of the risk of death from asthma. Furthermore, an increase in risk was much less apparent in the case of antiinflammatory asthma medications, which one might expect would be added to the treatment of patients with more severe disease that was not controlled with bronchodilator agents alone.

There are several possible explanations for the association between beta-agonists and death from asthma. We have already commented on the likelihood that patients for whom asthma medications are prescribed have more severe disease than other patients with asthma. A second possibility is that beta-agonists have adverse effects on organ systems other than the lungs. beta-Adrenergic agonists have long been under special scrutiny because of their potential for cardiotoxicity (Ref. 21) and their potential to induce hypokalemia (Ref. 22). A review of the available clinical information, however, suggests that at most 7 of the 44 deaths from asthma in our study might have been sudden and therefore possibly cardiac in origin. Rapidly progressive respiratory failure was much more common, as has been recently suggested by others (Ref. 23).

Recent evidence suggests that beta(sub 2)-agonists may make asthma worse, (Ref. 4) perhaps by increasing airway hyperresponsiveness (Ref. 24-26). According to this explanation, beta-agonists are precursors of severe asthma, possibly leading to death, so that distinguishing the relative effects of the disease and of its treatment is difficult in observational studies such as ours.

Clinicians should also remain alert to another possible mechanism -- that the benefits of beta(sub 2)-agonists for symptoms engender overreliance on this form of asthma management. If patients and their physicians are misled by the control of symptoms into thinking that the

patient's underlying asthma is stable, necessary anti-inflammatory treatment or other medications may be withheld while the patient's disease becomes life-threatening. Severe attacks of asthma may also become the rule with the use of beta-agonists if sensitivity to bronchoconstrictive agents is decreased while maximal airway narrowing is maintained, and attacks may occur more rapidly, as has recently been suggested (Ref. 27). Whatever the nature of the associations observed, whether they are causal relations or markers of severity, heavy use of these medications should send a clear signal to the patient and physician that the likelihood of a major adverse event is markedly increased and that further evaluation is needed.

We are indebted to the following members of the Scientific Advisory Board for reviewing the protocol for this study and the final report: Professors Peter Barnes (University of London), Bernard Begaud (University of Bordeaux), Nicholas Day (Cambridge University), Michael Hensley (Newcastle University, Australia), Michel Ibrahim, chairman (University of North Carolina), Helmuth Kewitz (Free University of Berlin), Albert Sheffer (Harvard University), and Stephen Walter (McMaster University); to Peter Burney (United Medical and Dental Schools-St. Thomas Hospital, University of London); and to many others whose dedication made this study possible, in particular Brenda Hemmelgarn, Lucie Blais, and Leah Lueck.

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?b 154

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            $7.80    0.100 Hrs File444
               $1.40  2 Type(s) in Format  3
               $1.00  1 Type(s) in Format  9
            $2.40  3 Types
    $10.20  Estimated cost File444
     $1.20  DIALNET
    $11.40  Estimated cost this search
    $11.64  Estimated total session cost   0.105 Hrs.

File 154:MEDLINE  1985-1993/SEP (9309W4)

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